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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,664	08/17/2001	Denise L. Faustman	DLF-002.1P	4530

7590 09/14/2005

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,664	FAUSTMAN, DENISE L.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-d 0

DETAILED ACTION

Status of claims

Pending claims 1-14 and 16-23 (amendment filed 6/25/2003) are under examination in the instant office action.

Claims 15 and 24-37 were canceled by applicant. [Paper No. 11 filed 6/25/2003].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 5 remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,081,030 (Civin) as explained in the prior office action as repeated herein.

Claims are directed to a method for inhibiting rejection by a host mammal of another mammal donor tissue wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen, step of transplanting the treated viable donor tissue into host mammal before MHC are re-expressed and step maintaining the treated viable donor tissue in the host mammal. Some claims are further drawn to donor and host mammals belonging to the same species. Some claims are further drawn to the use of tissue cells such as blood cells, precursor cell, bone marrow cells.

US 5,081,030 discloses a method for transplantation bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col.11, lines

30-35), step of transplanting the treated viable donor tissue into host mammal (col.11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). The cited patent clearly teaches that cells retain viability after enzymatic treatment. Both donor and host are rats or mammals belonging to the same species. The cited patent teaches that enzymatic treatment is intended to release cell surface molecules and that proteases including chymopapain and papain release cell surface proteins and glycoprotein antigens. The cited patent is considered to anticipate the claimed invention because it comprises identical active steps and, thus, the intended effects are reasonably expected to be identical as related to removal of antigens of MHC class I and to inhibition of donor tissue rejection, particularly in view that the cited patent demonstrates better survival of animals received engraftment of enzymatically treated cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 12-14 and 16-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 5,670,358 and US 6,156,306 as explained in the prior office action.

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen and steps of

transplanting and maintaining the treated viable tissue into/in the host mammal. Some claims are/are further drawn to the second transplanting step in the method for inhibiting transplant rejection. Some claims are further drawn to donor and host mammals belonging to the same or different species. Some claims are further drawn to host mammal being human. Some claims are further drawn to the use of tissues cells and/or organ parts such as blood cells, precursor cell, bone marrow cells, liver, brain, pancreas, kidney, etc. Some claims are further drawn to the use of enzyme papain and to the use of specific time and concentration for papain treatment of the donor tissue in the method for inhibiting transplant rejection

US 5,081,030 (Civin) teaches a method for transplantation of donor tissue cells that are enzymatically treated in order to remove surface molecules or glycoprotein antigens and it demonstrates better survival of host animals that received engraftment of the enzymatically treated donor tissue cells. The disclosure relates to graft vs. host disease (GVHD) and, thus, to inhibition of rejection of donor tissue by host recipient (col. 1, lines 26-33) as encompassed by the presently claimed invention. The cited patent demonstrates that increase of grafting cell doses result in better survival of engraftment recipients and, thus, US 5,081,030 suggests transplantation of additional or second donor tissues as encompassed by the present invention (claim 12). US 5,081,030 also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68).

In particular example, the cited patent US 5,081,030 (Civin) describes chymopapain enzymatic treatment of donor tissue before transplantation into host. However, it further teaches and suggests enzymatic treatment with proteases including chymopapain and papain in order to release cell surface proteins and glycoprotein antigens (col. 5, line 2). Although the cited patent

US 5,081,030 is silent that the enzymatically removed glycoprotein antigens are MHC class I antigens, the enzymes that are used in the method of US 5,081,0303 including papain remove MHC class I antigens as adequately demonstrated by Galati et al for papain (see abstract).

In particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor bone marrow tissue cells before transplantation into host. However, it also teaches and suggests a variety of cells that would be suitable for enzymatic treatment and transplantation including bone marrow, lymphocytes and hormone-secreting cells (col. 4, lines 8-10) and, thus, it suggests enzymatic treatment of tissue cells derived from various organs or organ part including pancreas, liver, kidney, brain, etc as encompassed by the claimed invention. In addition, US 5,670,358 is relied upon to demonstrate that hepatocytes and islets cells useful for transplantation are prepared by enzymatic treatment with chymopapain or papain (abstract).

The cited US 5,081,030 (Civin) teaches and demonstrates better survival of host animals that received engraftment of the enzymatically treated viable donor tissue cells but it is silent about re-expression of MHC class I antigens. However, US 6,156,306 demonstrates that cells treated with papain in order to remove MHC class I surface molecules will further re-express the MHC class I surface molecules (col. 16, lines 10-17).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the presently claimed invention drawn to transplantation of viable donor tissues treated with enzymes capable to remove antigenic glycoproteins belonging to MHC class I as it is taught and suggested by US 5,081, 030 with a reasonable expectation of success in inhibiting rejection by host mammal of donor tissue and improving host survival as demonstrated by US 5,081, 030 because enzymes used and suggested

in the method of US 5,081, 030 are capable to remove antigenic surface molecules including antigenic glycoprotein MHC class I as adequately demonstrated and taught by Galati et al. and US 6,156,306. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. It is considered to be within the purview of one of ordinary skill in the art to adjust time and concentration of enzymes including papain for treating donor tissues and for removal of antigenic molecules.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 1-14 and 16-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 5,670,358 and US 6,156,306 as applied to claims 1-9, 12-14 and 16-23 above, and further in view of Stone et al. (IDS reference; Transplantation. 1998. 65 (12) : 1577-1583) as explained in the prior office action..

Claims 1-9, 12-14 and 16-23 as explained above. Claims 10 and 11 are further drawn to the use of combination of papain and alpha-galactosidase in the method for inhibiting transplant rejection.

US 5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 6,617,171; US 5,670,358 and US 6,156,306 are relied upon as explained above.

In particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor tissue with one enzyme. However, it also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68).

Glycosidase such as or alpha-galactosidase is known to remove alpha-gal epitopes from xenografts and, thereby to alter immune response of host recipient.

For example: the reference by Stone et al. demonstrates that transplantation of xenografts treated with or alpha-galactosidase reduced inflammatory response of recipients (see abstract). The reference by Stone et al. [IDS-BJ] discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction of inflammatory reaction or immune response of recipient host (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was to combine papain and alpha-galactosidase for removal of antigenic and/or inflammatory cell surface molecules in the method for graft transplantations as suggested for generic protease and glycosidase by US 5,081,030 with a reasonable expectation of success in inhibiting rejection and reducing inflammatory host response because papain and alpha-galactosidase have been known and used in the prior art method for graft preparation and transplantation as adequately demonstrated by all cited references combined with Stone et al. One of skill in the art would have been motivated to combine two types of enzymes protease and glycosidase for the expected benefit in removing variety of cell surface antigenic structures as suggested by US 5,081,030. One of skill in the art would have been motivated to combine papain and galactosidase for the expected benefit in removing various surface antigenic structures because papain and alpha-galactosidase are taught and suggested as particularly useful enzymes for removal of antigenic cell surface structures that are MHC class I glycoproteins and that are

gal-epitopes respectively. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 7/14/2005 have been fully considered but they are not persuasive.

1. With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,081,030 (Civin) applicant argues that the Civin' reference is incapable of teaching critical recited steps of the Applicant's claims including step of enzymatic removal of MHC Class I antigens and step of transplantation of enzymatically treated cells into a host before re-expression of MHC Class I antigens (response pages 3-6) because the primary goal of the enzymatic treatment in the Civin' patent is intended for release of sorted cells from immunomagnetic microsphers.

The argument is not found convincing because Civin teaches that the cell suspension after enzymatic treatment is substantially free of receptor materials (for example: abstract) and that the enzyme degrades the cell surface ligand to which receptor is bound without substantially decreasing cell viability (for example: col. 4, lines 56-58). The particular teaching or particular statement cited by applicant at col. 3, lines 52-57, is one embodiment (col. 3, lines 47). Moreover, the disclosure that chymopapain treatment does not produce detectable damage clearly points out that cells remain viable as required by the Applicant's claims. The cells are

treated with identical enzymes as required by the claimed invention and, thus, the same surface structures including MHC Class I antigens are removed in the cited method as encompassed by the claims. Applicant appears to admit the inherent result of the enzymatic treatment (response page 5, par. 2, first line).

In one of the examples, the cited US 5,081,030 discloses a method for transplantation bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col.11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col.11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). The viable, enzyme-treated cells are reasonably expected to be capable to restore their biological structures and functions under conditions that that would maintain viability, grow and development of cells such as upon transplantation, for example. The viable cells are transplanted into host after enzymatic treatment. Thus, the cited method comprises step of transplantation of enzymatically treated cells into a host before re-expression of antigens including before re-expression of MHC Class I antigens within the meaning of the claims.

2. The cited patent US 6,617,171 (Faustman et al) has been removed from the combination of cited references in view of the Declaration by D.L Faustman filed 7/14/2005.

3. With regard to the claim rejection under 35 USC § 103 Applicant argue that the combination of cited references fails to present a suggestion of the claimed method (response pages 6-11).

As related to the Civin's patent (US 5.081,030) Applicant argues that it does not recognize removal of MHC Class I antigens (response pages 6-7). However, Civin clearly teaches and suggests removal of cell surface antigens with enzyme protease including chymopapain and papain (col. 5, line 2) and the enzymes that are used in the method of US 5,081,0303 including papain remove MHC class I antigens as adequately demonstrated by Galati et al for papain (see abstract).

As related to the Lee reference (US 5,670,358) Applicant argues that it teaches away since it teaches a method for inhibiting enzymatic effects on cells. However, the inhibition of enzymatic effects as taught by US'358 is intended to avoid excessive tissue digestion (col. 2, line 33) after enzymatic treatment or after enzymatic applications. In the office action, US 5,670,358 is relied upon to demonstrate that the presently claimed hepatocytes and islets cells useful for transplantation are prepared by enzymatic treatment with chymopapain or papain (abstract) in addition to a variety of cells that would be suitable for enzymatic treatment and transplantation taught and/or suggested in Civin's patent.

As related to US 6,156,306 (Brownlee et al.) Applicant argues that if fails to suggest "temporarily ablating" MHC Class I antigens from donor tissue because it is primary concerned with permanent effect resulting from cell transfection. However, the cited patent US 6,156,306 was/is relied upon to demonstrate that the cells treated with papain (but not transfected, for example: see col. 16, line 15) re-express the MHC class I surface molecules (col. 16, lines 10-17).

As related to the cited reference by Stone Applicant argues that the enzymatic treatment of graft tissues as disclosed therein includes the use of lethal agents such as ethanol that would

cause death of graft cells. However, alcohol is an additional agent. The reference by Stone et al. was/is relied upon to demonstrate that glycosidase such as or alpha-galactosidase is known to remove alpha-gal epitopes from xenografts in order to alter or to reduce immune response of host recipient upon transplantation.

Thus, the cited prior art combination teaches and/or suggests all critical limitations of the presently claimed method. Therefore, the claims are properly rejected under 35 USC § 103.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651

September 12, 2005

VERA AFREMOVA

PRIMARY EXAMINER